Original Article

Volume responsiveness assessed by passive leg raising and a fluid challenge: a critical review focused on mean systemic filling pressure

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Summary

This review applied cardiovascular principles relevant to the physiology of venous return in interpreting studies on the utility of a passive leg-raising manoeuvre to identify patients who do (responders) or do not respond to a subsequent intravenous volume challenge with an increase in cardiac output. Values for cardiac output, mean arterial and central venous pressure, and the calculated cardiovascular variables mean systemic filling pressure analogue, heart efficiency, cardiac power indexed by volume state and volume efficiency, before and after passive leg raising as well as before and after fluid volume challenge, were extracted from published studies. Eleven studies including 572 patients and 52% responders were analysed. Cardiac output increased by 12% in responders during passive leg raising and by 22% following a volume challenge. No statistically significant differences were found between responders and non-responders in cardiac output, mean arterial or central venous pressure before the passive leg-raising manoeuvre or the volume challenge. In contrast, the calculated mean (SD) systemic filling pressure analogue, reflecting the intravascular volume, was significantly lower in responders (14.2 (1.8) mmHg) than non-responders (17.5 (3.4) mmHg; p = 0.007) before the passive leg-raising manoeuvre, as well as before fluid volume challenge (14.6 (2.2) mmHg vs. 17.6 (3.5) mmHg, respectively; p = 0.02). The scalar measure volume efficiency was higher in responders at 0.35 compared with non-responders at 0.10. Non-responders also demonstrated deteriorating heart efficiency of −15% and cardiac power of −7% when given an intravenous fluid volume challenge. The results demonstrate that the calculation of mean systemic filling pressure analogue and derived variables can identify patients likely to respond to a fluid volume challenge and provides scalar results rather than merely a dichotomous outcome of responder or non-responder.

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Introduction

Recent reviews on fluid administration in critically ill patients highlight the importance of matching the right type of fluid to the right type of patient using the right type of monitoring for guidance at the right time [1, 2]. Volume responsiveness is pivotal to the management of fluid therapy, as only patients responding to expansion of the intravascular compartment with an

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increase in cardiac output may ultimately benefit by improved organ perfusion. Equally important, non-responders are harmed by excessive fluid loading, leading to cardiopulmonary congestion, tissue oedema and worse oxygenation. Administration of an intravenous fluid volume challenge is associated with an increase in cardiac output in only about half of haemodynamically unstable patients [3, 4].

A method to identify critically ill patients who are volume responsive is crucial to rational clinical fluid management. The central venous pressure (CVP) is still commonly used as a clinical estimate of the volume status [5], although its correlation with intravascular volume is unreliable and it is imprecise at predicting volume responsiveness [6, 7]. Low mean arterial pressure, or cardiac output, cannot in isolation be inferred to indicate volume responsiveness.

The assumption of a low cardiac output indicating volume responsiveness is entirely dependent on the inotropic state of the heart, and where it is operating on the Frank–Starling curve, as only a low-output state in the steep ascending portion of the curve is likely to be improved by fluid administration. Variations induced by positive pressure ventilation in arterial pressure, or related variables, have been investigated to guide volume therapy [8, 9]; however, these are restricted by the inherent physiological limitations of pressure changes to predict flow changes [10] and a number of prerequisite criteria that are rarely fulfilled in critically ill patients [11–14].

While CVP, mean arterial pressure and cardiac output in themselves are insufficient to establish whether a patient is volume responsive, they do allow a comprehensive description of the patient's haemodynamic state to be formulated. The stressed component of the total blood volume over the sum of all regional vascular compliances generates the mean systemic filling pressure, which reflects the effective circulating volume. The mean systemic filling pressure furthermore represents the driving pressure for venous return to the heart above right atrial pressure. The role of the heart and circulation may be seen as supporting the pressure gradient for venous return, by maintaining a low right atrial pressure and varying resistance to venous return. A measure of global cardiac performance, heart efficiency, is then given by the ratio of the pressure gradient for venous return and the mean systemic filling pressure. A ratio of 1 means that the mean systemic filling pressure operates against no back-pressure, and the venous return gradient optimally translates into cardiac output. Conversely, a ratio of 0 would be seen in circulatory arrest when all intravascular pressures equilibrate. Adding vascular resistance completes the description of cardiovascular function.

The methods and equations used to estimate a mean systemic filling pressure analogue (P_{msa}) when mean arterial pressure, CVP and cardiac output are known, as well as the heart efficiency (E_h) and the systemic vascular resistance have been described in detail elsewhere [15, 16]. These variables, their derivation and clinical utility, adhere to Guyton's original description of the regulation of cardiac output [17, 18] and have previously been explored in several clinical studies including assessments of intravascular volume [19–22].

The passive leg-raising manoeuvre is often promoted as a method to predict volume responsiveness by a reversible increase in venous return. Two recent systematic reviews and meta-analyses concluded that '*passive leg raising retains a high diagnostic performance (to identify volume responsiveness) in various clinical settings and patient groups*' [23] and that '*passive leg raising-induced changes in cardiac output very reliably predict the response of cardiac output to volume expansion in adults with circulatory failure*' [24]. Interestingly, in many of these studies, the haemodynamic status before passive leg raising was described by CVP, mean arterial pressure and cardiac output, but without any attempts to exploit this information further by calculating P_{msa}, E_h and systemic vascular resistance as descriptors of cardiovascular function.

In this review, we conceptually re-analysed published studies on volume responsiveness using passive leg raising and then a subsequent intravenous volume bolus. The aim was to illustrate how the calculated descriptors of the volume state, available before the passive leg raising, might be used for the purpose of determining volume responsiveness. We also studied the concordance of these variables between the passive leg-raising manoeuvre and acute intravascular volume expansion. Furthermore, we wanted to explore how those scalar variables could provide a continuous assessment of volume responsiveness, as opposed to

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the dichotomous description of the response to passive leg raising or a fluid bolus as merely responsive or non-responsive.

Methods

The PubMed, EMBASE, CINAHL databases and the Cochrane Database of Systematic Reviews were searched using the strings:

1 passive leg raising OR passive leg raise OR passive leg elevation OR passive leg lifting
2 fluid responsiveness OR fluid status OR fluid therapy OR volume OR volume status OR preload OR responsiveness OR resuscitation
3 #1 AND #2

No publication date restrictions were used, but only papers published in English were retrieved. The search was performed in January 2017 and updated in July 2017. We included all studies investigating passive leg raising in adults admitted to an intensive care unit, and using a specified fluid challenge to identify responders and non-responders by a cardiac output or stroke volume criterion. Data for the standard cardiovascular variables mean arterial pressure, CVP and cardiac output had to be reported separately at all steps of the study (i.e. before and after passive leg raising, before and after fluid challenge) and were collected as mean values. Information on the type of intensive care unit, patient inclusion criteria, cardiac output/stroke volume monitor, cut-off criterion for volume responsiveness, volume, type and infusion time for the fluid challenge, and the number of responders and non-responders was extracted. When height and weight of the subjects were not reported, we used mean values of 175 cm and 85 kg obtained from previous systematic reviews of volume responsiveness [6]. Three authors independently assessed eligibility for inclusion (KC, RS and AA).

The analogue mean systemic filling pressure (P_{msa}) was calculated as previously described [15] incorporating CVP, mean arterial pressure (MAP) and cardiac output (CO):

$$P_{msa} = 0.96 \times CVP + 0.04 \times MAP + c \times CO \quad (1)$$

The constant c has the dimensions of resistance and is determined by patient anthropometrics that scales the equation for patients of different height, weight and age. The normal mean systemic filling pressure is around 7 mmHg in humans [25] but higher in critically ill patients [26]. From Eqn 1, it is evident that any increase in the P_{msa}, reflecting an increased effective circulating volume, may be variably partitioned between CVP, mean arterial pressure and cardiac output. If the entire rise is in CVP, and none in mean arterial pressure or cardiac output, the patient is not volume responsive and, conversely, if the entire rise is in mean arterial pressure and cardiac output, the patient is maximally volume responsive. The typical patient will have a response between these extremes.

Cardiac output must equal the venous return that depends on the driving pressure ($P_{msa} - CVP$) and the resistance to venous return. The performance of the heart at any volume state can be expressed by the static heart efficiency, $E_{h,}$ [15]:

$$E_h = (P_{msa} - CVP)/P_{msa} \quad (2)$$

The ratio of a change in driving pressure for venous return over the change in P_{msa} represents a measure of the efficiency of a volume change to increase cardiac output, depending on where the cardiac function (Starling) curve intersects with the venous return curve [16, 20] and was termed volume efficiency, E_{vol}:

$$E_{vol} = \frac{\Delta(P_{msa} - CVP)}{\Delta P_{msa}} \quad (3)$$

The product of mean arterial pressure and cardiac output is referred to as cardiac power (CP) and provides an integrative measure of cardiac hydraulic pumping ability that correlates with clinical outcomes [27, 28]. The cardiac power reflects changes in intravascular volume [29] and when indexed to the volume state (CP_{vol}) may serve as a valuable marker to monitor volume responsiveness [20]. It was calculated as:

$$CP_{vol} = (CO \times MAP/P_{msa}) \times 0.0022 \quad (4)$$

The volume of the fluid challenge to identify responders and non-responders was specified in

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eligible studies. If the administered volume is assumed to be retained within the intravascular compartment for the duration of the study measurements, the volume given and the change in P_{msa} allow the vascular compliance, C_{vasc}, to be estimated by (indexed for body weight, bw):

$$C_{vasc} = \text{fluid challenge volume}/(\Delta P_{msa} \times \text{bw}) \quad (5)$$

The normal combined arterial and venous vascular compliance is in the range 1–2 $ml.mmHg^{-1}.kg^{-1}$ [30].

Haemodynamic variables were normally distributed according to the D'Agostino-Pearson omnibus normality test. The responses to passive leg raising and differences between responders and non-responders to the subsequent volume challenge were analysed using unpaired or paired t-tests as appropriate. The correlations between changes in the venous return driving pressure in response to the passive leg raising and volume challenge were described by the Pearson correlation coefficient. The associations between P_{msa} and E_{vol} and volume responsiveness were evaluated using the area under the curve for receiver operating characteristics (AUROC), including the standard error (SE). The criterion associated with the Youden index is reported with its 95%CI based on bootstrapping using 1000 replications. The sensitivity and specificity values are also reported with the 95%CI. The aggregate association between passive leg raising and volume responsiveness for all eligible studies was analysed by the summary receiver operating characteristics (SROC) [31], including SE, using patient numbers based on the sensitivity and specificity results in individual studies. The SROC was generated using MetaDisc v 1.4 (Unit of Clinical Biostatistics, Ramón y Cajal Hospital, Madrid, Spain) [32], and all other statistical analyses were performed using MedCalc v 12.3 (MedCalc Software, Ostend, Belgium). A p-value < 0.05 was considered significant for all statistical analyses.

Results

The literature search results are outlined in Figure 1. Eleven eligible studies were identified, which included 297 patients with an increase in cardiac output following a fluid volume bolus (responders) and 275 patients without an increase (non-responders) [33–43]. The

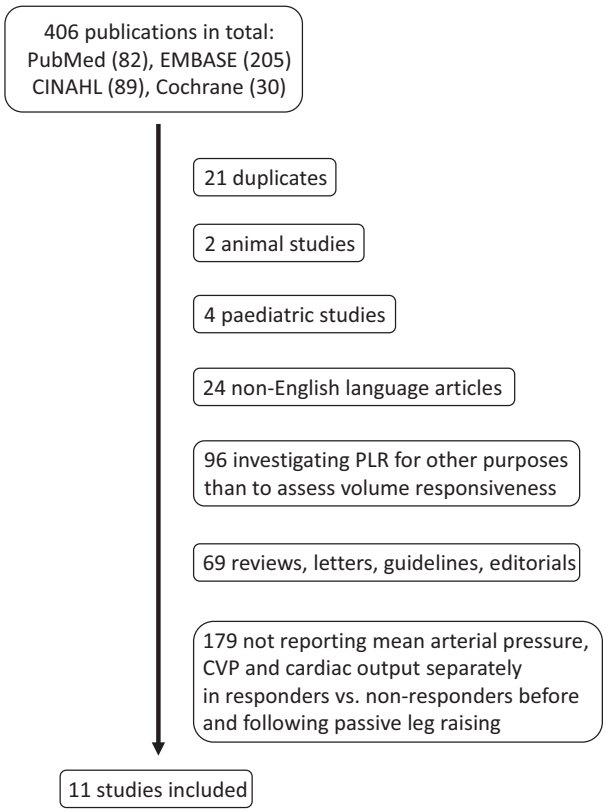

Figure 1 Overview of the literature search results.

characteristics of included studies are given in Table 1. The median (IQR [range]) volume of fluid was 500 (350–500 [250–500]) ml given over a median of 10 (10–15 [10–30]) min.

A summary of standard cardiovascular variables before and after passive leg raising split by responders and non-responders to the volume challenge is shown in Table 2. No statistically significant differences were demonstrated between the groups, although the cardiac output was numerically lower before passive leg raising in responders ($p = 0.09$). Passive leg raising induced an increase in mean arterial pressure, CVP and cardiac output and a decrease in systemic vascular resistance in responders.

Calculated cardiovascular variables before and after a passive leg raising are summarised in Table 3. Notably, P_{msa} was lower in responders at baseline before the passive leg raising and increased after passive leg raising to a value similar to that observed in non-responders. E_h and CP_{vol} were not significantly different between groups before or after the passive leg

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Table 1 Studies of volume responsiveness in response to a passive leg-raising manoeuvre.

Study	Setting	Indication for volume expansion	Cardiac output monitor	Criterion	Volume	Number	Proportion of responders
Thiel [41]	Medical ICU	Clinician's decision	Doppler ultrasound	SV >15%	500 ml rapid infusion	102	46%
Biais [33]	General ICU	SAP < 90 mmHg, HR > 100 min^{-1}, skin mottling, oliguria < 0.5 $ml.kg^{-1}.hr^{-1}$	TTE	SV > 15%	500 ml saline in 15 min	30	67%
Lakhal [40]	General ICU	SAP < 90 mmHg, MAP < 65 mmHg, skin mottling, oliguria < 0.5 $ml.kg^{-1}.hr^{-1}$, lactate > 2.5 mmol. l^{-1}, needing vasopressors	TCTD or TPTD	CO > 10%	300 + 200 ml modified fluid gelatin in 18 + 12 min	102	42%
Guinot [37]	Surgical ICU	Adult respiratory distress syndrome having venovenous extracorporeal membrane oxygenation	TTE	SV > 15%	500 ml saline in 15 min	25	52%
Dong [34]	Medical ICU	Severe sepsis, SAP < 90 mmHg, HR > 100 min^{-1}, skin mottling, oliguria < 0.5 $ml.kg^{-1}.hr^{-1}$, needing vasopressors	TPTD	SVI > 15%	500 ml 6% HES in 30 min	32	69%
Kupersztych-Hagege [39]	Medical ICU	SAP < 90 mmHg, HR > 100 min^{-1}, skin mottling, oliguria < 0.5 $ml.kg^{-1}.hr^{-1}$, lactate > 2 mmol. l^{-1}	TPTD	CI > 15%	500 ml saline in 10 min	48	40%
Xiao-ting [42]	Medical ICU	Septic shock, SAP < 90 mmHg, lactate > 4 mmol. l^{-1}, needing vasopressors	TPTD	CI ≥ 10%	500 ml saline in 15 min	48	71%
Guerin [36]	Medical ICU	Clinician's decision	TPTD	CI > 15%	500 ml saline in 10 min	30	50%
Fischer [35]	Surgical ICU	Post-cardiac surgery, clinician's decision for volume expansion	TPTD	CI > 15%	500 ml 6% HES in 15 min	78	71%
Kim [38]	Surgical ICU	Atrial fibrillation after cardiac valve surgery	Pulmonary artery catheter	SVI ≥ 10%	300 ml 6% HES in 5 min	43	35%
Xu [43]	General ICU	SAP < 90 mmHg, oliguria < 0.5 $ml.kg^{-1}.hr^{-1}$, tachycardia, lactate > 4 mmol. l^{-1}, needing vasopressors	Bioreactance	SV ≥ 10%	250 ml saline in 10 min	34	41%

ICU, intensive care unit; SV, stroke volume; SAP, systolic arterial pressure; HR, heart rate; TTE, transthoracic echocardiography; MAP, mean arterial pressure; TCTD, transcardiac thermodilution; TPTD, transpulmonary thermodilution; CO, cardiac output; SVI, stroke volume index; HES, hydroxyethyl starch; CI, cardiac index.

raising. In non-responders, the P_{msa} did not change following passive leg raising, while both E_h and CP_{vol} decreased. E_{vol} was more than three-fold greater in responders to the passive leg raising. Table 4 summarises calculated cardiovascular variables in responders and non-responders to volume challenge, with overall similar results as for the passive leg raising including lower baseline P_{msa} in responders. The E_{vol} was more than three-fold greater in responders than non-responders after the volume challenge.

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Table 2 Standard cardiovascular variables before and after a passive leg-raising manoeuvre, grouped by the subsequent response to volume expansion into non-responders and responders. Values are mean (SD).

	Before passive leg raising				After passive leg raising				p value before vs. after
	MAP mmHg	CVP mmHg	CO $l.min^{-1}$	SVR $dyn.s.cm^{-5}$	MAP mmHg	CVP mmHg	CO $l.min^{-1}$	SVR $dyn.s.cm^{-5}$	
Non-responders	76.3 (4.6)	10.3 (3.2)	6.2 (1.0)	866 (145)	78.3 (4.7)	12.4 (2.3)	6.3 (0.9)	851 (117)	0.37/0.13/ 0.48/0.35
Responders	73.1 (6.6)	8.5 (3.6)	5.9 (0.9)	905 (150)	79.2 (4.6)	11.2 (3.4)	6.6 (1.2)	846 (158)	< 0.001/ < 0.001/ < 0.001/0.007
p value	0.42	0.21	0.09	0.52	0.39	0.37	0.29	0.92	

MAP, mean arterial pressure; CVP, central venous pressure; CO, cardiac output; SVR, systemic vascular resistance.

No significant correlations were found between changes in P_{msa} – CVP, the driving pressure for venous return, induced by passive leg raising and changes induced by volume challenge, either in responders ($r = 0.44$, $p = 0.16$) or non-responders ($r = 0.40$, $p = 0.20$).

One study [36] was excluded from the SROC analysis as sensitivity and specificity results were not reported, leaving 10 studies including 542 patients. The SROC (SE) for passive leg raising studies was 0.89 (0.03) with a pooled sensitivity of 83% [95%CI 78–87%] and a pooled specificity of 79% [95%CI 74–84%] (Fig. 2). The AUROC for the association between P_{msa} at baseline before passive leg raising and the subsequent response to volume expansion in 11 studies was 0.87 (0.08), with the criterion $P_{msa} \leq 14.8$ mmHg having a sensitivity of 75% (95%CI 43–95%) and a specificity of 92% (95%CI 62–99%) to be associated with volume responsiveness (Fig. 3). The AUROC for the association between E_{vol} observed for the passive leg raising and the response to volume expansion was 0.89 (0.09), with the criterion > 0.07 having a sensitivity of 99% (95%CI 72–100%) and a specificity of 78% (95%CI 40–97%) to be associated with volume responsiveness (Fig. 4). The SROC was not significantly different from the P_{msa} AUROC ($p = 0.82$) or the E_{vol} AUROC ($p = 0.99$).

The mean C_{vasc} was significantly lower in responders at 1.7 (0.6) $ml.mmHg^{-1}.kg^{-1}$ compared with non-responders at 3.4 (3.0) $ml.mmHg^{-1}.kg^{-1}$ ($p = 0.04$).

Discussion

This conceptual re-analysis of studies investigating passive leg raising as a measure of volume responsiveness utilised additional cardiovascular variables that may be calculated when mean arterial pressure, CVP, cardiac output and anthropometric data are known. The calculated P_{msa} was significantly lower before passive leg raising in patients who were subsequently described as responders to a volume challenge, compared with non-responsive patients. The P_{msa} and the E_{vol}, providing information on the effective circulating volume and the efficiency of the autotransfused volume during passive leg raising to increase the driving pressure for venous return, were equally well associated with volume responsiveness. The ROC for these two variables was furthermore similar to the aggregate result from studies of the passive leg-raising manoeuvre. Volume responsive patients had lower vascular compliance compared with non-responsive patients. The investigated calculated cardiovascular variables offer additional and scalar information on volume responsiveness, bringing more nuance to fluid resuscitation than the simplistic binary outcome of responder or non-responder.

The mean systemic pressure analogue, P_{msa}, and in particular changes induced by fluid administration or patient position, have been demonstrated to correlate well with alternative estimates of this key volumetric variable [21]. The P_{msa} at baseline in both responders and non-responders was above the normal physiological value, but similar to previous reports in patients admitted to an intensive care unit [19–21, 26]. A key finding in this analysis was the significantly higher P_{msa} demonstrated in non-responders compared with responders, indicating a larger effective circulating volume at baseline before the passive leg raising. The

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Table 3 Calculated cardiovascular variables before and after a passive leg-raising manoeuvre, grouped by the subsequent response to fluid volume expansion into non-responders and responders. Values are mean (SD).

	Before passive leg raising			After passive leg raising				
	P_{msa} mmHg	E_h	CP_{vol} W.mmHg^{-1}	P_{msa} mmHg	E_h	CP_{vol} W.mmHg^{-1}	p value before vs. after	E_{vol}
Non-responders	17.5 (3.4)	0.42 (0.07)	27.9 (4.3)	18.5 (3.6)	0.34 (0.06)	25.8 (4.9)	0.10/0.01/0.04	0.08 ± 0.1
Responders	14.2 (1.8)	0.44 (0.08)	28.9 (5.2)	18.6 (3.7)	0.42 (0.06)	28.5 (4.8)	0.04/0.10/0.61	0.29 ± 0.1
p value	0.007	0.17	0.48	0.53	0.17	0.16		< 0.001

P_{msa}, mean systemic filling pressure analogue; E_h, heart efficiency; CP_{vol}, cardiac power indexed by P_{msa}; E_{vol}, volume efficiency.

Table 4 Calculated cardiovascular variables before and after fluid volume expansion, grouped as non-responders and responders. Values are mean(±SD).

	Before volume expansion			After volume expansion				
	P_{msa} mmHg	E_h	CP_{vol} W.mmHg^{-1}	P_{msa} mmHg	E_h	CP_{vol} W.mmHg^{-1}	p value Before vs. After	E_{vol}
Non-responders	17.6 (3.5)	0.41 (0.06)	27.8 (3.8)	19.8 (3.0)	0.35 (0.06)	25.9 (5.1)	0.10/0.02/0.01	0.10 ± 0.2
Responders	14.6 (2.2)	0.45 (0.08)	28.5 (4.9)	19.2 (3.6)	0.42 (0.05)	31.0 (4.2)	< 0.001/0.10/0.16	0.35 ± 0.1
p value	0.02	0.22	0.72	0.68	0.05	0.02		0.001

P_{msa}, mean systemic filling pressure analogue; E_h, heart efficiency; CP_{vol}, cardiac power indexed by P_{msa}; E_{vol}, volume efficiency.

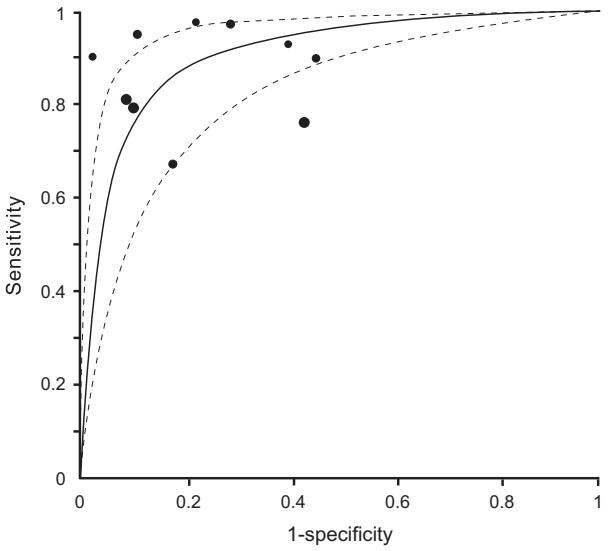

Figure 2 Summary receiver operating characteristic (SROC) curve for studies investigating the ability of haemodynamic changes during a passive leg-raising manoeuvre to predict a 10–15% increase in cardiac output following a subsequent volume challenge. Dashed lines = 95% CI.

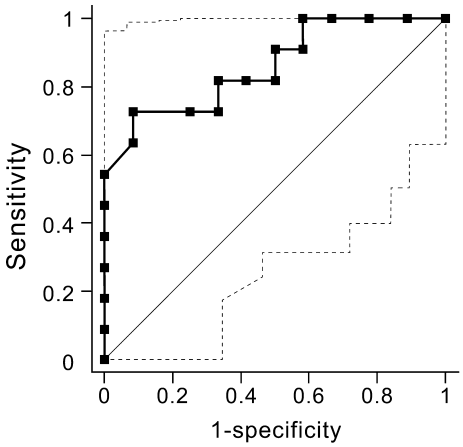

Figure 3 Receiver operating characteristic (ROC) curve for the association between the calculated mean systemic filling pressure analogue (P_{msa}) derived from baseline haemodynamic data before a passive leg-raising manoeuvre and an increase in cardiac output following a subsequent volume challenge. Dashed lines = widest sensitivity and specificity 95% CI for each node.

lack of a response to passive leg raising, as well as to further volume loading, might thus not be surprising. The standard cardiovascular variables mean arterial pressure, CVP and cardiac output are insufficient as comparators between groups to identify differences in effective baseline circulating volume. Numerically

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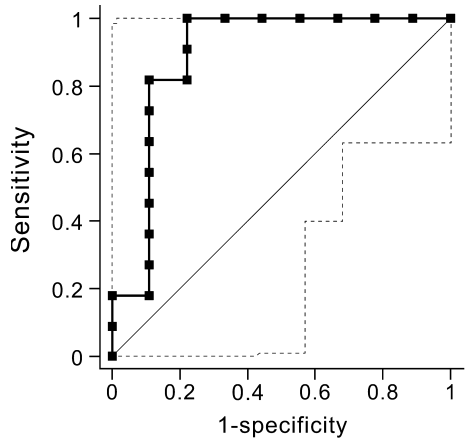

Figure 4 Receiver operating characteristic (ROC) curve for the association between the calculated volume efficiency variable (E_{vol}) derived from haemodynamic data during a passive leg-raising manoeuvre and an increase in cardiac output following a subsequent volume challenge. Dashed lines = widest sensitivity and specificity 95% CI for each node.

higher mean arterial pressure, CVP and cardiac output in non-responders at baseline, while not statistically different, all contributed to the higher calculated P_{msa}. The increase in P_{msa} during passive leg raising is consistent with the study by Guerin et al. that used an alternative technique to estimate mean systemic filling pressure [36].

The E_h and CP_{vol} were not significantly different between non-responders and responders at baseline, but importantly both decreased in non-responders after passive leg raising. Measures of cardiac performance were not different overall between responders and non-responders, meaning that cardiovascular function in responders was restored to the level of non-responders after an increase in their volume state. This is important as the P_{msa}, E_h and CP_{vol} variables in non-responders already at baseline could be used to guide alternative interventions to support cardiac output, rather than futile and potentially harmful volume expansion. The effects of passive leg raising are better described by the scalar and continuous E_{vol}, which in non-responders was only about a third of that observed in responders. The E_{vol} variable may therefore be used to assess the amount of a change after volume expansion, rather than just the presence of a change. This might enable the clinician to titrate inotropic agents and further intravenous volume administration.

The AUROCs for the associations between P_{msa} at baseline before passive leg raising and the E_{vol} following passive leg raising and volume responsiveness were not significantly different from the SROC of the passive leg raising studies. This supports the importance of the original volume state and the relevance of P_{msa}, including its use to derive the driving pressure for venous return. The utility of P_{msa} to ascertain the volume state is arguably encouraged by the demonstration of an association with volume responsiveness without the need for any further positional manipulation. The numerically lower AUROC for P_{msa} compared with SROC might reflect the limitations of the static variable P_{msa} compared with the dynamic changes assessed by passive leg raising, similar to other static circulatory pressures. Interestingly, the E_{vol} as measured from the response to passive leg raising had a slightly higher AUROC compared with P_{msa}.

Previous studies have indicated the importance of vasomotor tone for the P_{msa} [44] and for the changes in cardiac output during passive leg raising in septic patients [45]. The observation that C_{vasc} was lower in responders suggests that these patients had an increased vasomotor tone and an associated increase in the stressed volume, making them more responsive to the mobilisation of further volume during passive leg raising. The lack of a statistically significant correlation between passive leg raising and volume-induced changes in the venous return driving pressure might be expected, given the variable and largely unknown endogenous volume mobilised towards the central circulation during passive leg raising and the variable exogenous volumes used for a fluid challenge.

This conceptual re-analysis of published studies on the utility of passive leg raising to identify patients demonstrating volume responsiveness aimed to highlight the benefit of additionally derived cardiovascular variables available already during baseline conditions or after passive leg raising. The data used were obtained during different cardiovascular conditions, using different monitoring techniques and protocols to determine volume responsiveness. This heterogeneity, while potentially limiting the precision of the analyses, supports the pragmatic utility of P_{msa} and E_{vol}.

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Concurrent changes in E_h and CP_{vol} can be used as part of stopping rules for volume administration in non-responsive patients. The results do not call into question the previously published findings pertaining to the passive leg-raising manoeuvre but rather suggest an alternative viewpoint conducive to further developing haemodynamic assessments to guide diagnosis and treatment.

This review has important limitations, some of which are inherent to the nature of the included studies. Individual study cohorts were small, and patient characteristics as well as practices for cardiac output monitoring and volume challenges were heterogeneous. The time frame for measurements during passive leg raising was not reported. No individual data were available in the included studies, and only mean values were extracted. While the variance of the SROC reflects the total number of patients (n = 572), the variance for analyses based on calculated cardiovascular variables is based on the total number of studies (n = 11). Calculations relating to driving pressure for venous return assume that resistance to venous return did not change during interventions. The calculations of compliance assume that the administered volume remained in the intravascular space for the time span of repeat measurements, and are thus best regarded as estimates. The mathematical coupling between P_{msa} and cardiac output, inherent to the calculation of the former, may contribute to the association with cardiac output responses following volume expansion. Notwithstanding, the P_{msa} calculation, with the potential for prediction, is not linked to the change in cardiac output, used as the arbiter of the response.

In conclusion, the calculation of mean systemic filling pressure analogue and derived variables can identify patients likely to respond to a fluid volume challenge and provides scalar results beyond the dichotomous outcome of responder or non-responder. These variables, available when cardiac output, mean arterial pressure and CVP are known, warrant further clinical study as adjuncts to assessing volume responsiveness.

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